PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
80021-135		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 99/ 01057	29/10/1999	30/10/1998
Applicant		
THE UNIVERSITY OF BRITISH COLUMBIA et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   METHOD OF MODULATING CELL DIFFERENTIATION OR NEOPLASTIC TRANSFORMATION BY ALTERING CADHERIN-11 EXPRESSION OR FUNCTION

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 99/01057

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/705 A61K38/17 G01N33/574

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 646 250 A (SUZUKI SHINTARO) 8 July 1997 (1997-07-08) column 4, line 46 - line 52	
A	BUSSEMAKERS, MARION J. G. ET AL: "De novo expression of osteoblast (OB)- cadherin / 11 in prostate cancer." JOURNAL OF UROLOGY, (1996) VOL. 155, NO. 5 SUPPL., PP. 351A. MEETING INFO.: NINETY-FIRST ANNUAL MEETING OF THE AMERICAN UROLOGY ASSOCIATION ORLANDO, FLORIDA, USA MAY 4-9, 1996 , XP000909886 abstract	

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 June 2000	28/06/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chakravarty, A

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	BUSSEMAKERS, MARION J. G. ET AL: "Mesenchymal cadherins in prostate cancer development." EUROPEAN UROLOGY, (SEPT., 1998) VOL. 34, NO. 3, PP. 263. MEETING INFO.: 13TH CONGRESS OF THE EUROPEAN SOCIETY FOR UROLOGICAL ONCOLOGY AND ENDOCRINOLOGY INNSBRUCK, AUSTRIA OCTOBER 1-3, 1998 , XP000909885 abstract	
A	T SHIMAZUI ET AL: "Complex cadherin expression in renal cell carcinoma" CANCER RESEARCH,US,AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, vol. 56, no. 14, 15 July 1996 (1996-07-15), pages 3234-3237-3237, XP002125347 ISSN: 0008-5472 page 3236 -page 3237	
P,X	CHEN G.T.C. ET AL: "Antisteroidal compounds and steroid withdrawal down-regulate cadherin - 11 mRNA and protein expression levels in human endometrial stromal cells undergoing decidualisation in vitro." MOLECULAR REPRODUCTION AND DEVELOPMENT, (1999) 53/4 (384-393). , 24 June 1999 (1999-06-24), XP002139413 abstract	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CA 99/01057

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5646250 A	08-07-1997	US 5597725 A	28-01-1997
		CA 2111573 A	28-10-1993
		EP 0604603 A	06-07-1994
		JP 7500019 T	05-01-1995
		WO 9321302 A	28-10-1993
		US 5639634 A	17-06-1997

WHAT IS CLAIMED IS:

1. A method of modulating differentiation or neoplastic transformation of cells by causing said cells to increase or decrease cad-11 expression or function.

2. The method of claim 1 wherein said modulation is of differentiation or neoplastic transformation of the cell.

3. The method of claim 1 wherein said modulation is for preventing or terminating a pregnancy, and said method comprises decreasing cad-11 function or expression in trophoblast cells.

4. The method of claim 1 wherein said modulation is for reducing the viability of carcinoma cells having a low to moderate metastatic potential, and said method comprises decreasing cad-11 expression or function in the cells.

5. The method of any one of claims 1-4 wherein cad-11 expression is increased by hormone treatment of the cells.

6. The method of any one of claims 1-4 wherein cad-11 function is decreased by contacting the cells with an agent that interferes with cad-11 function.

7. The method of claim 6 wherein said agent is an anti-cad-11 antibody.

8. The method of any one of claims 1-4 wherein cad-11 expression is decreased by contacting the cells with an agent that interferes with cad-11 expression.

9. The method of claim 8 wherein said agent prevents transcription to or translation of, cad-11 mRNA.

10. The method of claim 9 wherein said agent is an antisense oligonucleotide.

11. The method of claim 10 wherein said oligonucleotide comprises an oligonucleotide substantially identical to, or which will hybridize to SEQ ID NO:1.

12. The method of claim 4 wherein said carcinoma cells are prostate tumor cells.

13. The use of a hormone for preparation of a medicament for use in the method of any one of claims 1-12

14. The use of an agent that interferes with cad-11 function for preparation of a medicament for use in the method any one of claims 1-12.

15. The use according to claim 14 wherein said agent is an anti-cad-11 antibody.

16. The use of an agent that interferes with cad-11 expression for preparation of a medicament for use in the method of any one of claims 1-12.

17. The use of claim 16 wherein said agent is an antisense oligonucleotide which prevents transcription to, or translation of cad-11 mRNA.

18. The use of claim 17 wherein said oligonucleotide comprises an oligonucleotide substantially identical to, or which will hybridize to SEQ ID NO:1.

19. A method for assessing the metastatic potential of carcinoma cells comprising: contacting cells in a tissue sample suspected of containing a carcinoma with a detectable indicator capable of binding to cad-11 or cad-11 mRNA; and, determining the presence or absence of cad-11 expression in the tissue.

20. The method of claim 19 wherein said detectable indicator comprises an oligonucleotide.

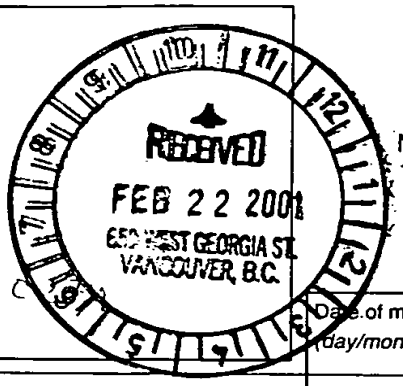
PATENT COOPERATION TREATY

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

ROBINSON, J. Christopher
SMART & BIGGAR
Box 11560, Suite 2200
650 West Georgia Street
Vancouver, BC V6B 4N8
CANADA
FAX: (604) 652 - 0



PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	16.02.2001
Applicant's or agent's file reference 80021-135	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/01057	29/10/1999	30/10/1998

Applicant
THE UNIVERSITY OF BRITISH COLUMBIA et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Faux, K Tel.+49 89 2399-8062

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
80021-135		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/01057	29/10/1999	30/10/1998
International Patent Classification (IPC) or national classification and IPC C07K14/00		
Applicant THE UNIVERSITY OF BRITISH COLUMBIA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/04/2000	16.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Chakravarty, A Telephone No. +49 89 2399 8536

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/01057

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-31 as originally filed

Claims, No.:

1-21 with telefax of 23/12/2000

Sequence listing part of the description, pages:

1,2, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8,11,12,16,18-21
	No:	Claims	1-7,9,10,13-15,17
Inventive step (IS)	Yes:	Claims	8,11,12,16,18-21
	No:	Claims	1-7,9,10,13-15,17
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the report

Sequence listing pages 1 and 2 are part of the application as originally filed.

The amendments filed with the letter dated 22.12.00 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

Claim 3: applicant submits that basis is to be found on page 31, lines 7-10, however, this passage is concerned only with prostate cancer cells whereas the claim is not so limited.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application concerns methods for modulating differentiation or neoplastic transformation of cells by causing the cells to increase or decrease cad-11 (cadherin 11) expression or function.

Novelty

Claims 1-7, 9, 10, 13-15, 17 are not novel because known methods fall within their scope. The art contains an extremely large number of documents relating to methods of modulating differentiation or neoplastic transformation of cells. Moreover, the link between cad-11 and prevention or termination of pregnancy appears to be via known methods (e.g. gonadal steroids, or RU486 see Chen et al, Molecular reproduction and development, 1999-06-24, 53 (4), 384-393). The discovery of the underlying mechanism does not confer novelty on known methods.

The methods of claim 8, using anti cad-11 Abs and claims 11 and 12 which specify antisense oligonucleotide (SEQ ID 1) for decreasing cad-11 expression, are novel.

Inventive step.

Although there is ample prior art linking both differentiation and neoplastic growth and metastasis (see the cited "A" documents in the ISR), to cad-11 there is no

indication in the art that methods modulating cell growth using these particular approaches would succeed, the same applies to methods for preventing or terminating pregnancy.
Hence, inventive step can be recognised for subject-matter which fulfils the conditions below:

The claims should be restricted to methods which include details of the means to achieve the required result. Claims will only meet the requirements of novelty and inventive step if they address specifically identified, novel means for increasing or decreasing cad-11 expression or function.

Claims 1-13 are directed to methods of treatment of the human or animal body by therapy.
No unified criteria exist in the PCT for the assessment of the presently worded claims on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for instance, does not recognise as industrially applicable claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for the first use in medical treatment and the use of such a compound in the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

Claim 6: The expression "a hormone that increases cad -11 expression or function" is unclear because it attempts to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

Claims 1-7, 9, 10, 13-15 and 17 relate to methods are drafted in such a way as to attempt to define the subject-matter in terms of the result to be achieved. Indeed, the claims are directed to a particular mechanism of action. The use of such a formulation renders the claims unclear in scope (Art. 6 PCT) and is not justified by

the disclosed means of achieving the desired result. The application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methods. Furthermore, it is possible to define the subject-matter in more concrete terms (e.g. as in claims 8, 11 and 12). The above claims therefore do not satisfy the requirements of Article 6 PCT.

Incorporation by reference is regarded as unclear (Article 6). Hence, the incorporations by reference throughout the description of the present application should be replaced by a short summary of the document in question. However the summary must be confined to merely reproducing the relevant content of the prior art document.

What is claimed is:

1. A method of modulating differentiation or neoplastic transformation of cells by causing said cells to increase or decrease cad-11 expression or function.

2. The method of claim 1 wherein said modulation is of differentiation or neoplastic transformation of the cell.

3. The method of claim 1 wherein said modulation is for reducing the invasiveness of carcinoma cells having a high metastatic potential, the method comprising increasing cad-11 expression or function in the cells.

4. The method of claim 1 wherein said modulation is for preventing or terminating a pregnancy, and said method comprises decreasing cad-11 function or expression in trophoblast cells.

5. The method of claim 1 wherein said modulation is for reducing the viability of carcinoma cells having a low to moderate metastatic potential, and said method comprises decreasing cad-11 expression or function in the cells.

6. The method of claim 3, wherein the cells are treated with a hormone that increases cad-11 expression or function.

7. The method of any one of claims 1, 2, 4 and 5, wherein cad-11 function is decreased by contacting the cells with an agent that interferes with cad-11 function.

8. The method of claim 7 wherein said agent is an anti-cad-11 antibody.

9. The method of any one of claims 1, 2, 4 and 5, wherein cad-11 expression is decreased by contacting the cells with an agent that interferes with cad-11 expression.

10. The method of claim 9 wherein said agent prevents transcription to or translation of, cad-11 mRNA.

11. The method of claim 10 wherein said agent is an antisense oligonucleotide.

12. The method of claim 11 wherein said oligonucleotide comprises an oligonucleotide substantially identical to, or which will hybridize to SEQ ID NO:1.

13. The method of claim 5 wherein said carcinoma cells are prostate tumor cells.

14. The use of a hormone for preparation of a medicament for use in the method of claim 6.

15. The use of an agent that interferes with cad-11 function for preparation of a medicament for use in the method of claim 7 or 8.

16. The use according to claim 15 wherein said agent is an anti-cad-11 antibody.

17. The use of an agent that interferes with cad-11 expression for preparation of a medicament for use in the method of claim 9 or 10.

18. The use of claim 17 wherein said agent is an antisense oligonucleotide which prevents transcription to, or translation of cad-11 mRNA.

19. The use of claim 18 wherein said oligonucleotide comprises an oligonucleotide substantially identical to, or which will hybridize to SEQ ID NO:1.

20. A method for assessing the metastatic potential of carcinoma cells comprising: contacting cells in a tissue sample suspected of containing a carcinoma with a detectable indicator capable of binding to cad-11 or cad-11 mRNA; and, determining the presence or absence of cad-11 expression in the tissue.

21. The method of claim 20 wherein said detectable indicator comprises an oligonucleotide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
80021-135		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA99/01057	29/10/1999	30/10/1998
International Patent Classification (IPC) or national classification and IPC C07K14/00		
Applicant THE UNIVERSITY OF BRITISH COLUMBIA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

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   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
20/04/2000	16.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Chakravarty, A Telephone No. +49 89 2399 8536

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA99/01057

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-31 as originally filed

Claims, No.:

1-21 with telefax of 23/12/2000

Sequence listing part of the description, pages:

1,2, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

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- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

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- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	8,11,12,16,18-21
	No:	Claims	1-7,9,10,13-15,17
Inventive step (IS)	Yes:	Claims	8,11,12,16,18-21
	No:	Claims	1-7,9,10,13-15,17
Industrial applicability (IA)	Yes:	Claims	1-21
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the report

Sequence listing pages 1 and 2 are part of the application as originally filed.

The amendments filed with the letter dated 22.12.00 introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 34(2)(b) PCT. The amendments concerned are the following:

Claim 3: applicant submits that basis is to be found on page 31, lines 7-10, however, this passage is concerned only with prostate cancer cells whereas the claim is not so limited.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application concerns methods for modulating differentiation or neoplastic transformation of cells by causing the cells to increase or decrease cad-11 (cadherin 11) expression or function.

Novelty

Claims 1-7, 9, 10, 13-15, 17 are not novel because known methods fall within their scope. The art contains an extremely large number of documents relating to methods of modulating differentiation or neoplastic transformation of cells. Moreover, the link between cad-11 and prevention or termination of pregnancy appears to be via known methods (e.g. gonadal steroids, or RU486 see Chen et al, Molecular reproduction and development, 1999-06-24, 53 (4), 384-393). The discovery of the underlying mechanism does not confer novelty on known methods.

The methods of claim 8, using anti cad-11 Abs and claims 11 and 12 which specify antisense oligonucleotide (SEQ ID 1) for decreasing cad-11 expression, are novel.

Inventive step.

Although there is ample prior art linking both differentiation and neoplastic growth and metastasis (see the cited "A" documents in the ISR), to cad-11 there is no

indication in the art that methods modulating cell growth using these particular approaches would succeed, the same applies to methods for preventing or terminating pregnancy.
Hence, inventive step can be recognised for subject-matter which fulfils the conditions below:

The claims should be restricted to methods which include details of the means to achieve the required result. Claims will only meet the requirements of novelty and inventive step if they address specifically identified, novel means for increasing or decreasing cad-11 expression or function.

Claims 1-13 are directed to methods of treatment of the human or animal body by therapy.
No unified criteria exist in the PCT for the assessment of the presently worded claims on the question whether they are industrially applicable, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claims. The EPO, for instance, does not recognise as industrially applicable claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for the first use in medical treatment and the use of such a compound in the manufacture of a medicament for a new medical treatment.

Re Item VIII
Certain observations on the international application

Claim 6: The expression "a hormone that increases cad -11 expression or function" is unclear because it attempts to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

Claims 1-7, 9, 10, 13-15 and 17 relate to methods are drafted in such a way as to attempt to define the subject-matter in terms of the result to be achieved. Indeed, the claims are directed to a particular mechanism of action. The use of such a formulation renders the claims unclear in scope (Art. 6 PCT) and is not justified by

the disclosed means of achieving the desired result. The application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such methods. Furthermore, it is possible to define the subject-matter in more concrete terms (e.g. as in claims 8, 11 and 12). The above claims therefore do not satisfy the requirements of Article 6 PCT.

Incorporation by reference is regarded as unclear (Article 6). Hence, the incorporations by reference throughout the description of the present application should be replaced by a short summary of the document in question. However the summary must be confined to merely reproducing the relevant content of the prior art document.